REMARKS

Amendments

Claims 1-23 are pending.

Claim 9 is amended herein to incorporate the inadvertently omitted term "screening." Support may be found generally throughout the application, for example, at column 3, line 57, and Claims 1, 14, and 19 as filed. This amendment is made to make the claims more consistent and definite, and is not intended to limit the scope of Claim 9 in any way.

No new matter is added.

Reissue Application Incorporates Changes in Certificate of Correction

The Examiner requested Applicants to enter the changes in the Certificate of Correction into the body of the reissue application. Applicants have made the requested change in the copy of the reissue application filed herewith. Applicants thank the examiner for noting in a telephone conversation on August 30, 2005 that the Examiner considers that the changes are not extensive and therefore the Examiner is not requiring a clean copy of the application to be submitted with a petition under 37 C.F.R. § 1.183. (M.P.E.P. 1411.01).

Invention Disclosure Statement

Entry of the invention disclosure statement (IDS) filed herewith and acknowledgement of the references cited therein is respectfully requested.

Supplementary Reissue Declaration

Filed herewith is a supplemental reissue declaration executed by inventors Cox and Ewart. Because inventor Gage is deceased, also enclosed is a declaration supplemental sheet (Form PTO/SB/LR2) executed by the legal representative of deceased inventor Gage. Entry of the supplemental reissue declaration and declaration supplemental sheet filed herewith is respectfully requested.

Power of Attorney

Also enclosed is a new power of attorney. Entry of the Power of Attorney by Assignee and Election of Assignee to Conduct Prosecution to Exclusion of Inventors filed herewith is respectfully requested.

Rejection under 35 U.S.C. § 251—Supplemental Reissue Declaration

The Examiner rejects Claims 1-23 under 35 U.S.C. 251 as being improperly broadened in a reissue application sworn to by the assignee and not the patentee. The Examiner notes the reissue declaration filed March 11, 2004 is defective.

Applicants enclose herewith supplemental reissue declarations executed by inventors Cox and Ewart, and the legal representative of deceased inventor Gage. Because the original declaration was defective, this supplemental declaration again states the error upon which the reissue is based and also states that the error arose without any deceptive intention on the part of the applicants. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a) over Harpold et al. US 5,846,757 and Schubert et al.

The Examiner rejects claims 9, 11, 12, 13, 14, 16, 17, 18, 19, 21, 22 and 23 under U.S.C. § 103(a) as being unpatentable over US 5,846,757 (hereinafter the '757 patent) and Schubert et al. American Society for Microbiology 1995, page 63 (hereinafter the Schubert et al. reference). Applicants respectfully traverse.

The claimed invention is a screening method for determining ion channel modulating activity of a test substance having potential for such modulating activity (independent Claims 9, 14 and 19).

Included in the claimed method is a step of contacting a host cell with the test substance, said host cell expressing HIV-1 Vpu integral membrane protein in the plasma membrane, said protein having ion channel activity when expressed as a heterologous protein in the plasma membrane of the host cell (representative step from Claim 14).

However, the '757 patent does not teach or suggest screening a test substance having potential for modulating the activity of any viral protein, let alone the ion channel activity of HIV-1 Vpu when expressed as a heterologous protein in the plasma membrane of a host cell. The '757 patent is directed to Ca^{2+} channel proteins, which are native to the plasma membrane in some bacterial, fungal, and plant cells ('757, column 1, lines 27-31). The '757 patent is particularly directed to Ca^{2+} channels in mammalian (human) cells.

Also included in the claimed method is a step of determining changes to the ion channel activity of said heterologous protein induced by the test substance (Claims 9, 14 and 19). The changes to the ion channel activity of the heterologous protein induced by the test substance are determined by detecting the effect of the test substance on changes in permeability of the plasma membrane of the host cell to small cellular metabolite molecules (Claim 9), or detecting the effect of the test substance on changes in net movement across the plasma membrane of the host cell of small cellular metabolite molecules (Claim 14).

By contrast, the '757 patent, teaches direct electrophysiological measurement of ion channel current. Such methods typically employ complex, delicate analytical apparatus and can be "too tedious and time-consuming for routine screening of ion channel activity" (present application, column 2, lines 48-52). Further, the '757 patent also requires a step of "depolarizing the cell membrane of said cell" ('757, Claim 1 and column 23, lines 43-44).

The '757 patent also teaches measurement of ion channel activity via intracellular detection of a large "indicator protein", which additionally requires incorporation into the cell of a transcriptional control element operatively linked for expression to a structural gene that encodes the indicator protein ('757, column 13, lines 54-67).

By contrast, the claimed method measures ion channel activity **indirectly** through changes in permeability of the plasma membrane of the host cell to **small** cellular metabolite molecules. The present application teaches that these changes can be measured by simple methods such as cross-feeding of cells which are auxotrophic for the small metabolite molecule of interest. Therefore, the claimed method does not require the complex electrophysiological or

intracellular methods taught by the '757 patent. Moreover, the claimed methods eliminate the depolarization step of the '757 patent.

The Schubert et al. reference refers to electrophysiology and provides no additional teaching regarding ion channel activity measurement beyond that of the '757 patent. Thus, the Schubert et al. reference does not cure the deficiencies of the '757 patent.

The Examiner also states that one of ordinary skill in the art would have had a reasonable expectation of success for heterologous expression of the HIV-1 Vpu protein of the Schubert et al. reference in the method of the '757 patent to elucidate the effects HIV-1 Vpu infection has on cellular ion channel function and to identify compounds that modulate HIV-1 Vpu ion channel activity.

However, the Schubert et al. reference and the '757 patent do not teach or suggest heterologous expression of HIV-1 Vpu integral membrane protein in the **plasma membrane**, said protein having ion channel activity. It is well known in the art that heterologous expression of membrane proteins can result in problems that lead to loss of activity such as incorrect folding, aggregation to form inclusion bodies, and the like. HIV-1 Vpu is not native to plasma membranes but "associates with the Golgi and endoplasmic reticulum membranes in infected cells, but has not been detected in the plasma membrane nor in the viral envelope" (present application, column 2, lines 53-57). There is no teaching or suggestion in the Schubert et al. reference or the '757 patent to express HIV-1 Vpu as a heterologous protein in the plasma membrane of a host cell, nor any direction as to how to successfully achieve such expression to result in ion channel activity. There is no teaching that HIV-1 Vpu expressed outside its native membrane would fold correctly or retain its native ion channel activity. Thus, there is no reasonable expectation of success.

Further, the Schubert et al. reference does not teach or suggest a test substance having potential for ion channel modulating activity, let alone a screening method for determining the modulating ability of such a substance on HIV-1 Vpu. Rather, the Schubert et al. reference is directed to mutations which permanently block activity of HIV-1 Vpu. There is no teaching or

suggestion in the Schubert et al. reference of test substances which can reversibly modulate (i.e., increase, decrease, or maintain) the ion channel activity of HIV-1 Vpu.

Both the '757 patent and the Schubert et al. reference are silent regarding "small cellular metabolite molecules." The term "small cellular metabolite molecules" (including, for example, proline or adenine; present application, column 3, lines 41-42) is distinct from the components employed in the '757 patent, which are atomic ions selected for by calcium channel proteins (e.g., Ca^{++}, Ba^{++}) and large molecules such as the indicator protein.

Because both the '757 patent and the Schubert et al. reference are silent regarding "small cellular metabolite molecules" they cannot teach or suggest a relationship between such molecules and ion channel activity. Thus, the cited references, alone or combined, cannot teach or suggest the claimed method step of determining the changes to the ion channel activity of the heterologous protein induced by the test substance by detecting the effect of the test substance on changes in permeability of the plasma membrane of the host cell to small cellular metabolite molecules.

Therefore, the claimed invention is nonobvious over the '757 patent and the Schubert et al. reference, and Applicants respectfully request withdrawal of the corresponding rejection under U.S.C. § 103(a).

Rejection under 35 U.S.C. § 103(a) Further in View of Tribe, US 4,681,852

The Examiner rejects claims 13, 18, and 23 under U.S.C. § 103(a) as being unpatentable over the '757 patent and the Schubert et al. reference, further in view of Tribe, US 4,681,852 (hereinafter the '852 patent). Applicants respectfully traverse.

As detailed above, the combined teachings of the '757 patent and the Schubert et al. reference fail to teach or suggest all the limitations of the claimed invention because these references fail to disclose methods for screening test substances for ion channel activity by using a host cell which expresses HIV-1 Vpu as a heterologous protein in its plasma membrane. The '852 patent does not cure these deficiencies of the '757 patent and the Schubert et al. reference

The '852 patent teaches enhancing the production of aromatic amino acids such as phenylalanine in various strains of cells expressing aroP mutants. The aroP gene "specifies the common aromatic transport system, which is involved in transport of each of the three aromatic amino acids; phenylalanine, tryptophan and tyrosine" ('852, column 30, lines 55-57).

The Examiner states that one of ordinary skill in the art "would have been motivated to detect the leakage of metabolites in the method of Harpold et al. by cross-feeding autotrophic [*sic*] cells because Tribe teaches that this technique is specifically useful for identifying mutant cells with a particular loss of a relevant transport system."

However, the '852 patent's teaching of aromatic transport proteins is not relevant to ion channel proteins. One of ordinary skill in the art knows that there are substantial differences in size, electronic properties and chemical properties (e.g., hydrophobicity/hydrophilicity) between the atomic ions which are selected for by ion channel proteins (e.g., Ca^{++}, Ba^{++} in the '757 patent) and the aromatic groups selected for by aromatic transport proteins (e.g., phenylalanine, tryptophan and tyrosine in the '852 patent). These differences are reflected in the substantial differences in sequence, structure and function between ion channel proteins and aromatic transport proteins. Thus, there is no motivation to combine the '757 patent and the '852 patent.

Further, because the '757 patent does not teach transport (leakage) of small metabolite molecules, there is no motivation to try the methods of the '852 patent to detect such molecules. Also, the '852 patent only teaches the use of the cross-feeding technique for identifying aromatic transport system mutations in cells. The '852 patent does not teach that cross feeding can determine changes to the ion channel activity of a heterologous protein induced by a test substance.

Moreover, the '852 patent specifically teaches **away** from a functional relationship between the common aromatic transport system and atomic ions similar to those selected for by the ion channel proteins in the '757 patent. The '852 patent investigates the addition of iron and cobalt ions to the growth media ('852, column 44, line 37 to column 45, line 8) and concludes that there is "**no apparent iron effect** on either cell growth or phenylalanine output over the range of ferric chloride concentrations tested" and further "the effect of adding a range of

cobaltous chloride concentrations (5-400 μM CoCl2) to culture medium was examined but **no clear evidence was obtained that this parameter has any effect** on phenylalanine yield" (emphasis added). Consequently, contrary to the Examiner's assertion, there would not have been a reasonable expectation of success for cross-feeding the auxotrophs of the '757 patent by the method of the '852 patent because the '852 patent teaches that there is no functional relationship between the common aromatic transport system and atomic ions similar to those selected for by the ion channel proteins in the '757 patent.

Finally, even in combination, the '757 patent, the Schubert et al. reference and the '852 patent still do not teach or suggest the claimed step of determining the changes to the ion channel activity of the heterologous protein induced by the test substance by detecting the effect of the test substance on changes in permeability of the plasma membrane of the host cell to small cellular metabolite molecules.

Therefore, the invention is nonobvious over the Schubert et al. reference and the '757 patent, further in view of the '852 patent. Applicants respectfully request withdrawal of the rejection under U.S.C. § 103(a).

Allowable Subject Matter

Applicants acknowledge the Examiner's determination that Claims 1-8, 10, 15, and 20 are drawn to allowable subject matter.

Conclusion

For the reasons set forth above, Applicants submit that all the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims of this application at an early date is earnestly solicited.

Pursuant to 37 CFR §1.136, Applicants hereby petition that the period for response to the action dated June 13, 2005, be extended for two months to and including November 13, 2005.

Accompanying this amendment is a Petition for Extension of Time and a check for $60 for the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: November 11, 2005

Kraig K. Anderson
Reg. No. 54,961

Fish & Richardson P.C.
500 Arguello Street, Suite 500
Redwood City, California 94063
Telephone: (650) 839-5070
Facsimile: (650) 839-5071

50291524.doc